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Insect Juvenile Hormone Mimics: A Chemical Metamorphosis from Terpenoid Esters to Aryloxy-Dioxolanes

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Abstract. The 1,3 dioxolane derivative **5** is a potent juvenile hormone mimic. The stereoselective synthesis of its stereoisomers **6–9** was based on the chiral glycerol derivative **12**. Three different approaches to this central compound **12** were investigated: using chiral building blocks, enantioselective catalytic hydrogenation, and stereoselective crystallization. The latter is the most suitable for large scale synthesis. *In vivo* testing of the different stereoisomers on *Nauphoeta cinerea* showed that the juvenoid activity is mainly associated with the (2*R*,4*S*)-**6** isomer.

Introduction

Since their discovery in the late 60's [1a–c], the insect juvenile hormones (JH's, **1**) drew the attention of many research laboratories at universities and in industry [1d–g]. Besides intensive work on the synthesis and the biological activity of the natural JH's efforts were concentrated on the development of mimics possessing an increased chemical and metabolical stability as well as a pronounced biological activity and selectivity [2]. A major research breakthrough was achieved by the replacement of the, for practical purposes unstable epoxy-containing sesquiterpene unit in the natural JH's **1** by a phenoxyphenoxy moiety (**2**) [3]. Further modifications led to **3** and the commercially successful compound **4** [4]. Milestones of this development are illustrated by the *Formulae* **1–5**.

In the present article we describe the synthesis of a very potent 4-phenoxy-phenoxy JH-mimic, 2-ethyl-4-[4-(3-fluorophenoxy)phenoxy]methyl-1,3-dioxolane (**5**), as well as the influence of the stereochemistry on the biological activity of its stereoisomers **6–9** as insect growth regulators.

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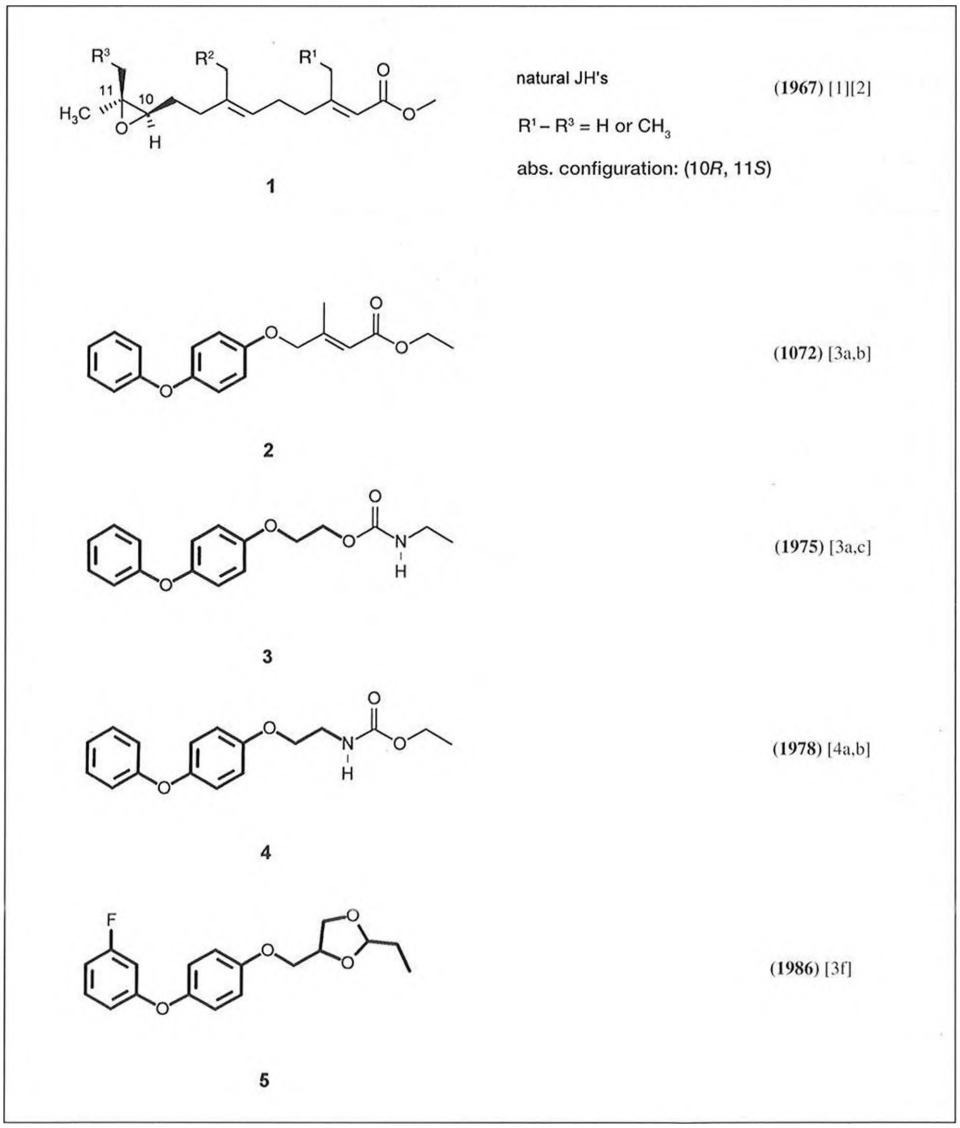
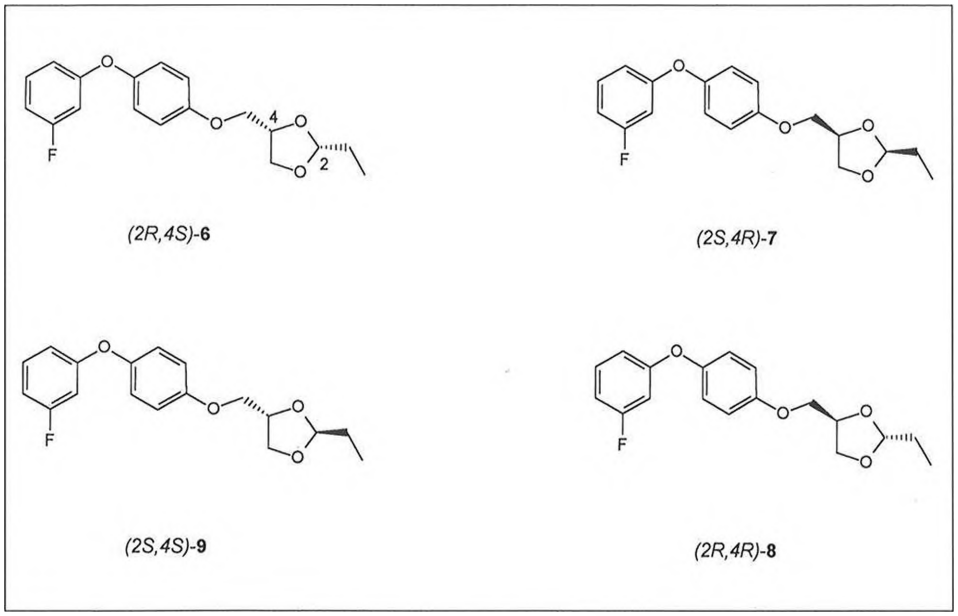
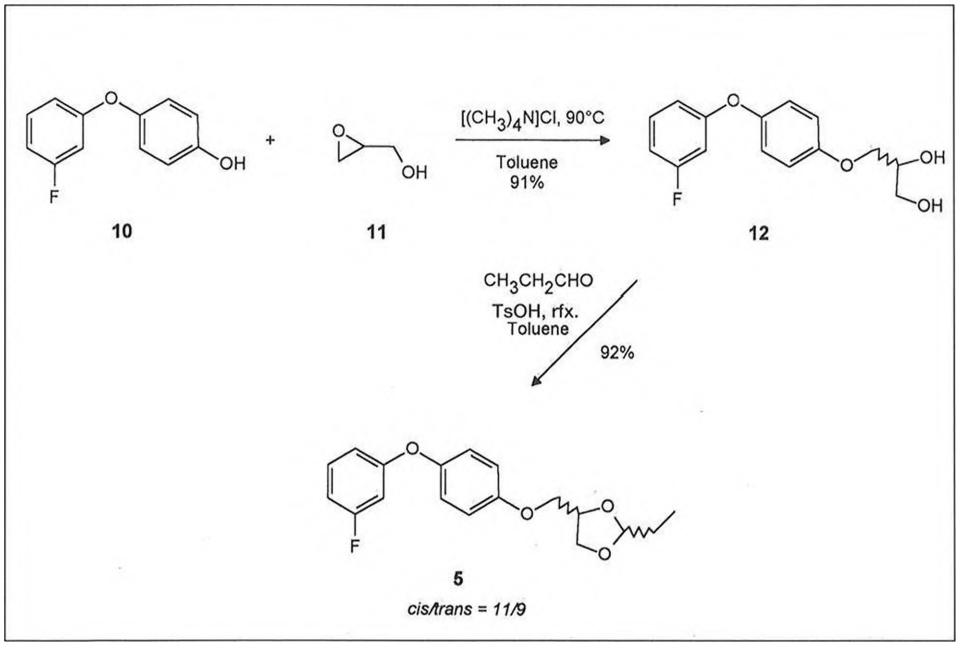
The nonselective synthesis of 5 [3f] involves the reaction of 4-(3-fluorphenoxy)phenol (**10**) [5] with glycidol (**11**) catalyzed by a quaternary ammonium salt. Acid-catalyzed acetalization of the obtained diol **12** with propanal affords a 11:9 mixture of the *cis* and *trans* diastereoisomeric acetals **5** [6] which were separated by chromatography on silica gel. Testing the *cis*- and *trans*-racemates showed that activity as insect growth regulator was mainly associated with the racemate *cis*-**5**. In order to determine the influence of the absolute configuration [7] on the biological activity, an enantioselective entry to the *cis*-stereoisomers (2*R*,4*S*)-**6** and (2*S*,4*R*)-**7** was needed [8].

The chiral glycerol derivative (2*R*)-**12** was the central compound in the chosen approach to the target structures. Three different enantioselective syntheses of (2*R*)-**12** were investigated: a classical chiral building block approach, an enantioselective catalytic approach [9], and a nonconventional stereoselective crystallization approach [9].

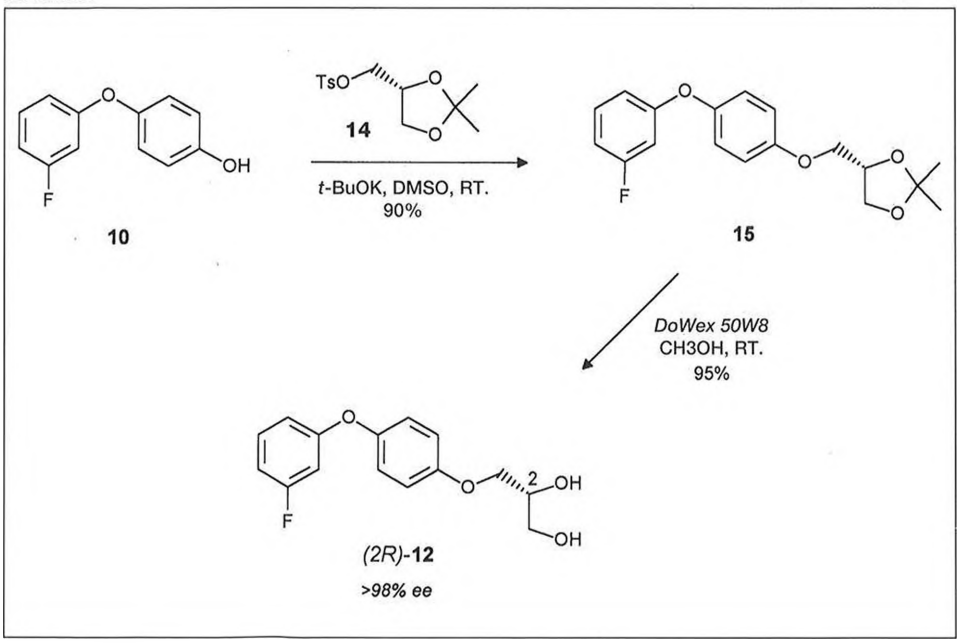




Scheme 1



Scheme 2



The 'Chiral-Pool' Approach (*Scheme 2*)

The base-mediated substitution of the tosylate by the phenoxy-phenoxy group of **10** in the commercially available C_3-chiral building block **14** afforded, after acid-catalyzed methanolysis of the resulting dimethyldioxolane **15**, the desired diol (2*R*)-**12** in 85% overall yield and *e.e.* >98%. The first step of this very straightforward process is very sensitive to the base and solvent used. For instance, the use of NaH in DMF decreases the yield of this substitution to 40–50%.

Enantioselective Catalytic Hydrogenation (*Scheme 3*)

The enantioselective catalytic hydrogenation of functionalized ketones to the corresponding highly enantiomerically pure hydroxy compounds has made impressive progress in recent years [10].

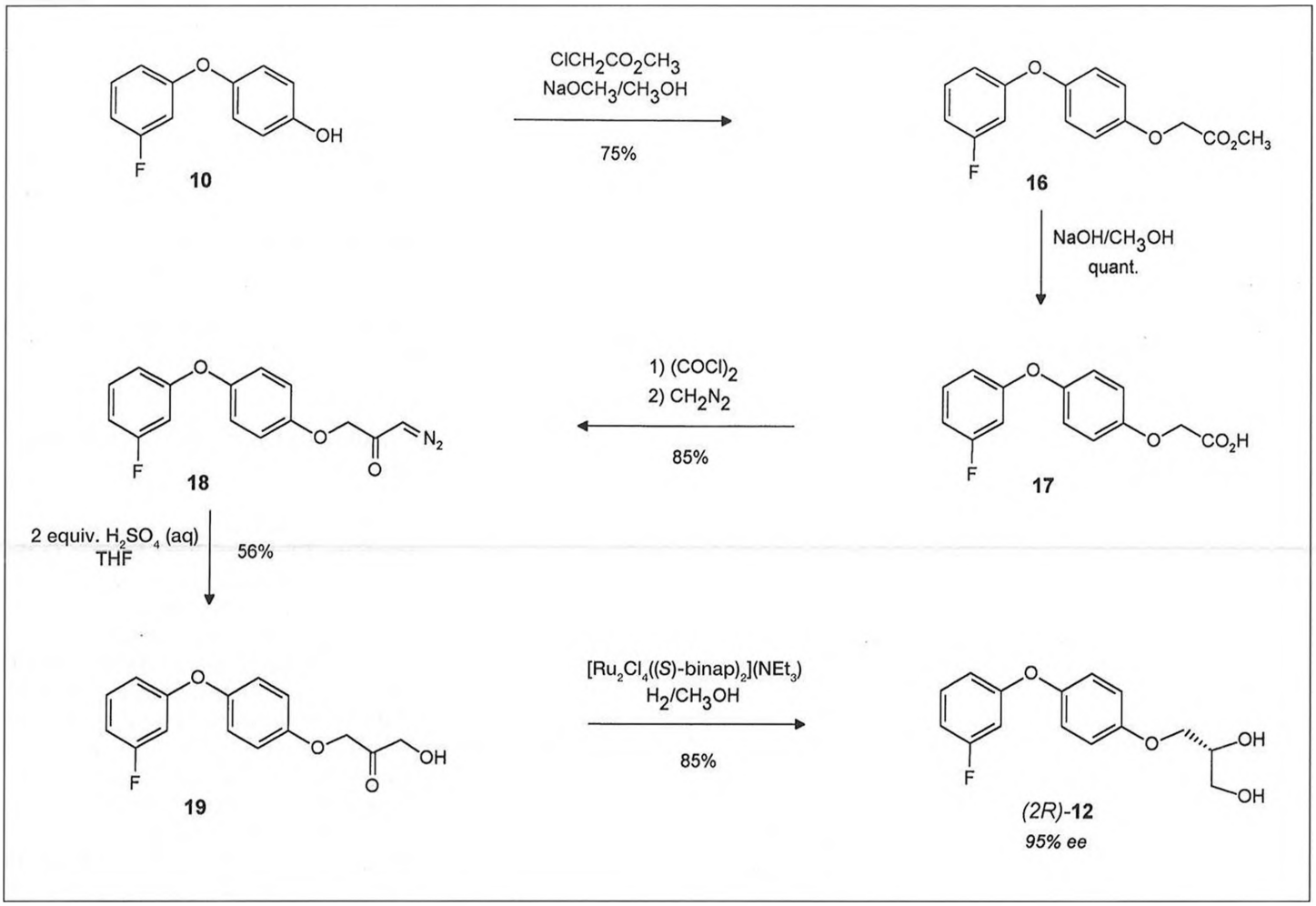
The α-hydroxy-ketone **19** was considered as a suitable substrate to be hydrogenated to (2*R*)-**12** using Ru-binap catalysts [10]. It was synthesized in the following straightforward manner. Treatment of 4-(3-fluorphenoxy)phenol (**10**) [5] with methyl chloroacetate in the presence of base afforded the methyl-aryloxy-acetate **16** [11] in 75% yield. The latter was converted into the α-diazoketone **18** (*via* **17**) using standard procedures [12]. Treatment of **18** with aqueous H_2SO_4 in THF led to the desired α-hydroxy ketone **19** in a moderate yield [13]. The key step, the enantioselective hydrogenation of **19** to the diol (2*R*)-**12**, proceeded smoothly in high chemical and optical yields (85%, *e.e.* >95%) [9] with $[Ru_2Cl_4((S)\text{-binapP})_2](NEt_3)$ [14] as catalyst.

Stereoselective Crystallization (*Scheme 4*)

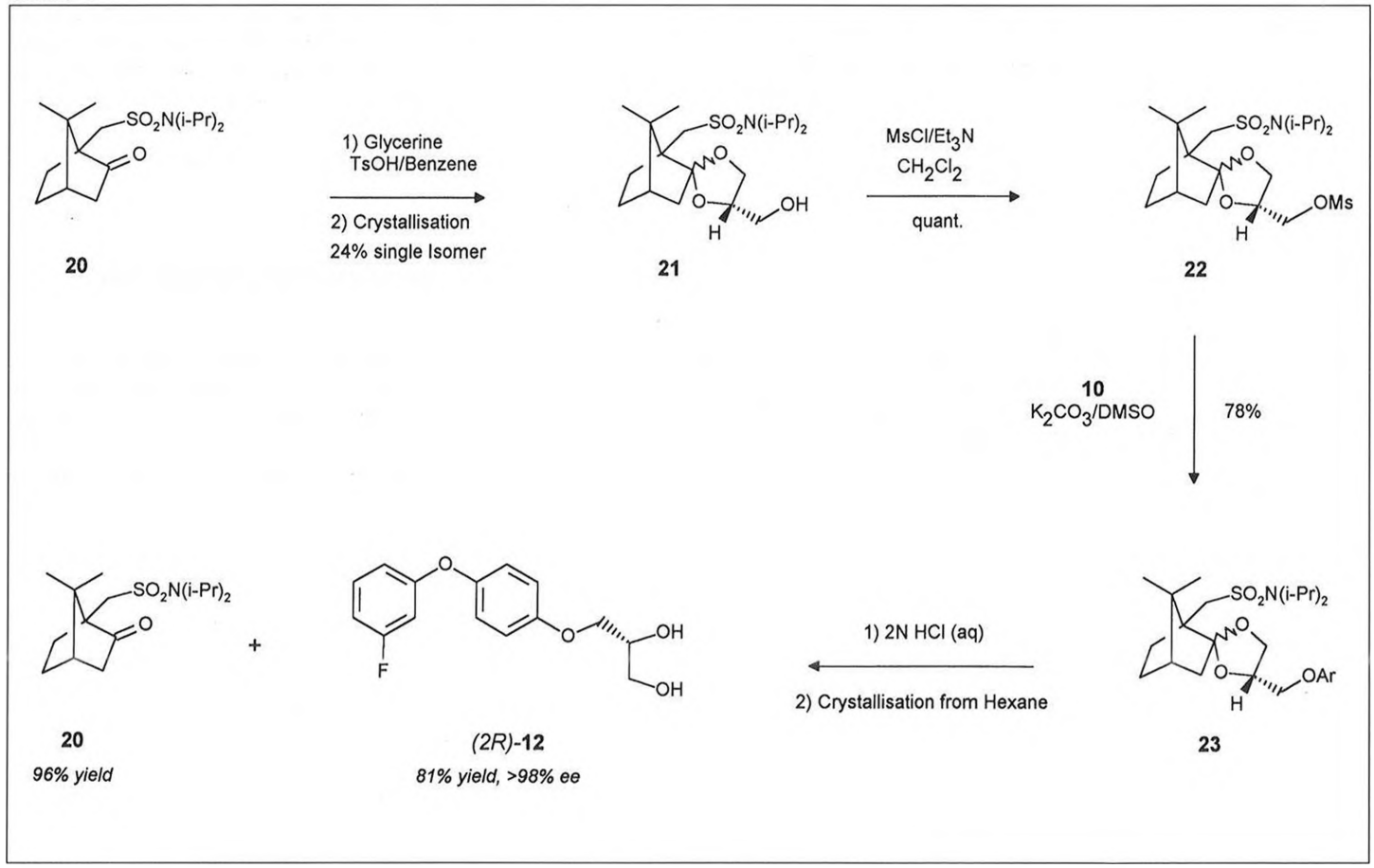
After having established two practicable laboratory scale approaches to the diol (2*R*)-**12**, we turned our attention to the preparation of enantiomerically enriched propanediol derivatives using *N,N*-diisopropyl-10-camphorsulfonamide as chiral auxiliary [15], a method well-suited for scale-up.

In order to obtain the required (2*R*)-configuration in the target molecule, the (1*R*)-camphor-10-sulfonamide **20** [16] was used as starting material. In analogy to described procedures [15], one diastereoisomeric acetal **21** was formed preferentially (38% and 59% based on conversion, resp.) upon acetalization of (1*R*)-**20** with glycerol under acid catalysis. The acetal **21** was isolated in diastereoisomerically

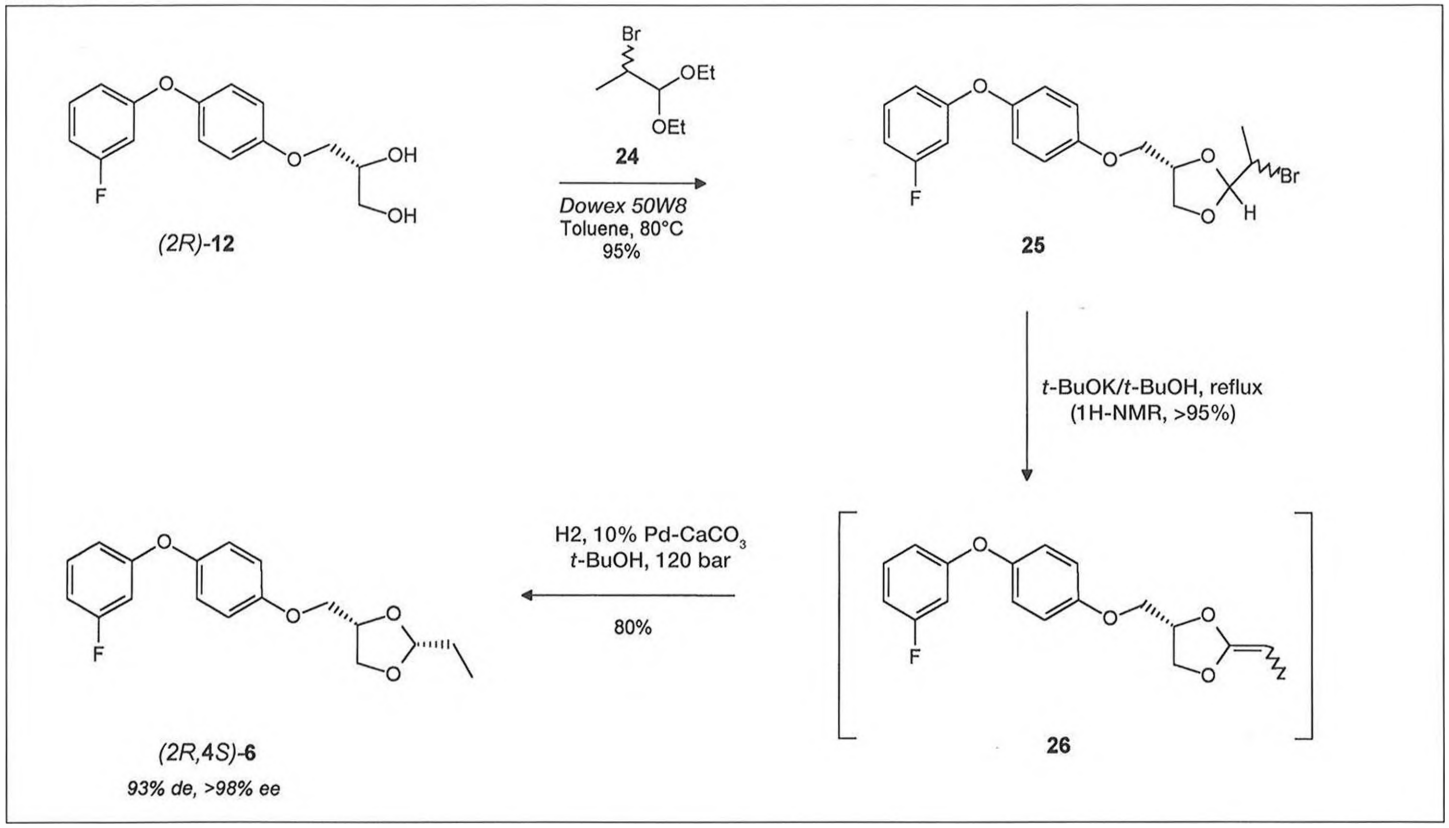
Scheme 3



Scheme 4



Scheme 5



pure, crystalline form. In spite of extensive optimization attempts, full conversion of (1*R*)-**20** could never be achieved. However, the mixture of the three minor diastereoisomeric acetals could be equilibrated under the above acetalization conditions to a mixture of all four diastereoisomers containing again *ca.* 60% of the desired crystalline isomer **21**. The free hydroxy group in **21** was substituted by 4-(3-fluorphenoxy)phenol [5] using standard procedures [9]. Hydrolysis of the aryl ether **23** to the diol (2*R*)-**12** and the auxiliary **20** was carried out using aqueous acid in CH_3OH. From the crude mixture of the two reaction products the diol (2*R*)-**12** was isolated in high chemical and optical yields (81%, *e.e.* >98%) by crystallization from hexane. The chiral auxiliary (1*R*)-**20** was recovered from the mother liquors in almost quantitative yield [9].

The described approach to the diol (2*R*)-**12** fulfills the requirements for a large-scale process, assuming the acetalization step can be brought to high efficiency either through full conversion or by recycling of the minor isomeric products.

At this stage of the work, small isomerically pure samples of all four isomers **6**–**9** for laboratory scale biological testing were obtained by acetalization of enantiomerically pure (2*R*)- or (2*S*)-**12** with propanal, and subsequent chromatographic separation of the *cis*- and *trans*-stereoisomers on silica gel. In order to obtain preparative amounts of the desired *cis*-

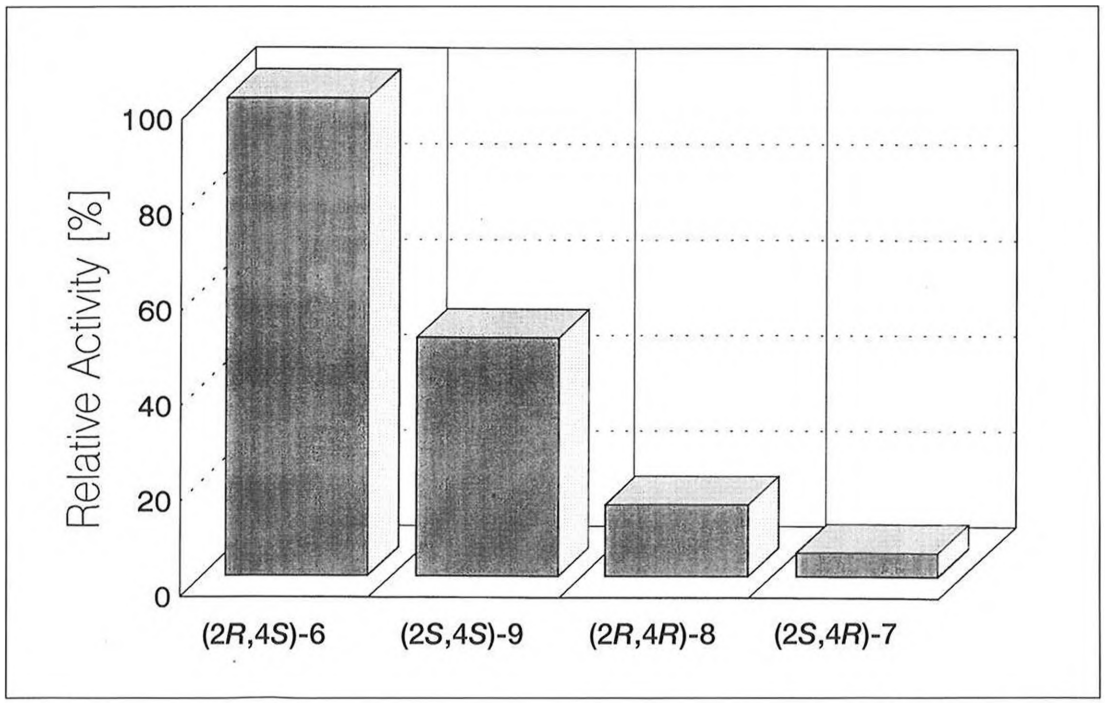


Figure. In vivo *activity of the dioxolane stereoisomers against* Nauphoeta cinerea

stereoisomers in the target disubstituted dioxolanes, we focused our efforts on irreversible, stereoselective dioxolane formation.

Ketene-acetal Hydrogenation
(*Scheme 5*)

The face-selective heterogeneous catalyzed hydrogenation of an appropriate ketene-acetal proved to be the best solution to this problem. Acid-catalyzed transacetalization of α-bromo-propionaldehyde-diethylacetal (**24**) [17] with the diol (2*R*)-**12** afforded the bromoethyl-dioxolane **25** in good yield. Elimination of HBr with *t*-BuOK in *t*-BuOH and *in situ* hydrogenation of the ketene acetal **26** using 10% $Pd/CaCO_3$ as catalyst gave the desired *cis*-2,4-disubstituted 1,3-dioxolane **6** in gram-scale, in 80% yield with d.e. = 93%.

In vivo Juvenoid Activity (*Fig.*)

The biological activity as juvenoids of the isomers of the dioxolane **5** was assessed *in vivo* on the cockroach *Nauphoeta cinerea* on the basis of differences in size, shape, and coloration of various body parts (*e.g.* wings) which are known to be under the control of juvenile hormone [18]. The different isomers were injected in olive oil solution into pre-adult stages (nymphes). The evaluation of the juvenoid activity was based on five different morphological characteristics, each of which were quantified using a scoring system.

According to the observed morphological effects, the studied dioxolanes clearly act as juvenoids. In the low-dose range (<0.5 μg/insect), this activity is even superior to that of natural juvenile hormone III. This is probably due to a higher metabolic stability of the synthetic compound. The relative activities of the four stereoisomers of **5** are summarized in the *Figure*.

Apparently, the configuration at C(4) of the dioxolane ring is of major relevance for the biological activity of the isomers of **5**. In this context, it was also demonstrated, that there is no epimerization at C(2) at biological pH values.

The *in vivo* biological activity is mediated by the juvenile hormone receptor, which has a high preference for the natural (10*R*)-isomer of juvenile hormone compared to the (10*S*)-isomer [18]. It is interesting to note that, in a competition assay with the radiolabeled natural juvenile hormone the hormone carrier protein in the insect's hemolymph did not at all bind any of the isomers of the juvenoid dioxolane **5**.

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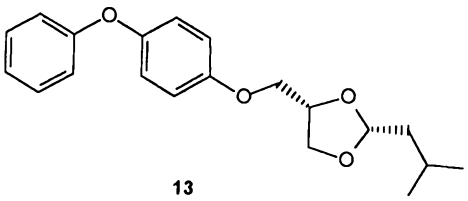
[6] The configuration in this series of 2,4-disubstituted 1,3-dioxolanes was determined by X-ray structural analysis of the crystalline derivative **13** [7]. The correlation to other compounds in this series was then performed by ^{13}C-NMR analysis.



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[8] Below, the synthetic work will be described for the (2*R*)-aryloxy-glycerol series. All the discussed reactions were also performed with the corresponding (2*S*)-isomer with almost identical chemical and optical yields. The e.e.'s were determined by HPLC chromathography on a *Chiralcel-OD* (Daicel) column: hexane/2-propanol, 1 ml/min, UV-detection at 230 nm.

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